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(54) Title: COMPOSITION, CONTAINING SUBLIMED SULPHUR, FOR ALTERING PLASMA HOMODYST(E) LEVELS IN HUMANS

(57) Abstract

Plasma homocysteine values > 10.2μmol per litre are associated with an increased risk of atherothrombosis, but normal values are considered to be 4 to 15 μmol per litre. An initial test subject with Hyper–homocystinemia and lactose intolerance was treated with Sublimed Sulfur 300 mg orally twice daily for 45 days. An additional 46 randomly selected subjects were treated with Sublimed Sulfur 200 mg orally daily for 30 days. Basal control plasma homocysteine, erythrocyte folic acid and serum vitamin B12 and lipids were compared with follow–up results obtained 24 hours and 30 days after discontinuation of Sublimed Sulfur. In the initial test subject, basal plasma homocysteine of 77 μmol per litre decreased by 95.7 percent. In the 46 patients, the effect of Sublimed Sulfur varied according to the initial basal plasma homocysteine concentration; basal levels of 2.3 to 7 μmol per litre increased by 58.5 percent ($p < 0.001$) 24 hours after discontinuation of treatment, and by 85.4 percent 30 days later; basal levels of 7.1 to 9.9 μmol per litre showed no consistent changes, and basal levels of 9.9 to 22.1 μmol per litre decreased to 63.9 percent ($p < 0.005$) of basal levels 24 hours after discontinuation of Sublimed Sulfur, and to 70.7 percent of basal levels 30 days later. Sublimed Sulfur therapy eliminated the initial plasma homocysteine differences between low, intermediate and high basal levels. Sublimed Sulfur therapy normalized plasma homocysteine by causing a regression towards the mean of basal plasma homocysteine levels.

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COMPOSITION, CONTAINING SUBLIMED SULPHUR, FOR ALTERING PLASMA HOMODYST(E) LEVELS IN HUMANS

DESCRIPTION

Background Hyper-homocysteinemia is a risk factor for venous thrombosis and atherothrombosis of the coronary, carotid, cerebral, central and peripheral arteries.[1-13] Elevated plasma homocysteine concentrations have been reported in chronic renal failure,[14-15] hypothyroidism, pernicious anemia,[16] advancing age and several types of carcinoma, including breast, ovarian and pancreatic,[17] and in deficiencies of vitamin B12, folic acid,[18-19] vitamin B6,[20] methionine synthase and cystathionine-Beta-synthase.[21] The complications due to atherothrombosis are reported to be associated with plasma homocysteine concentrations > 10.2 μmol per litre[22] but the normal laboratory values are considered to be 4 to 15 μmol per litre.[23] The apparent contradiction between plasma homocysteine concentrations reported to be normal and the values associated with an increased risk of atherothrombosis suggested that one or more additional factors may be necessary for alteration of plasma homocysteine concentrations. Elemental sulfur, an integral component of the sulfur-containing essential amino acids and sulfur-containing enzymes, was considered to be a possible necessary factor, and a clinical study was undertaken to determine the effect of orally administered elemental Sulfur on the Sulfur -containing essential amino acid, homocysteine. Orally administered Sublimed Sulfur USP, and also precipitated sulfur, has been mixed with molasses and used as a laxative.[24-26]

Methods An initial test subject with hyper-homocysteinemia of 77 μmol per litre was treated with Sublimed Sulfur. An additional 46 subjects, 31 men and 15 women were randomly selected. The subjects had single or multiple diagnoses of generalized atherosclerosis, hypertension, myocardial infarction, angina pectoris, peripheral vascular disease, coronary angioplasty, diabetes mellitus, hyperlipidemia, hypothyroidism, past history of carcinoma, hiatus hernia, osteoarthritis and osteoporosis, depression, obstructive airways disease, bronchial asthma, essential tremour, hiatus hernia and the postmenopausal state. A 30 day course of Sublimed Sulfur 200 mg, 1 capsule orally pc breakfast daily, was added to existing medical therapy which was continued unchanged for the duration of the study. Each subject's basal plasma homocysteine was compared with results obtained 24 hours and 30 days after discontinuation of Sublimed Sulfur. Basal and follow-up comparisons were also made for erythrocyte folic acid and serum levels of vitamin B12 and lipids. The subjects did not receive betaine, vitamin B12, folic acid and vitamin B6 during the course of the study.

The Wilcoxon T test was used to evaluate the quantitative data. Numerical values indicate the mean and standard error of the mean.

Results The initial test subject's basal plasma homocysteine of 77 μmol per litre decreased by 95.7 percent. In the 46 additional subjects, the effect of the Sublimed Sulfur varied according to the initial basal plasma homocysteine concentration; low basal plasma homocysteine levels generally increased and

high basal plasma homocysteine levels usually decreased after completion of the 30 day course of Sublimed Sulfur; basal levels of 2.3 to 7 μmol per litre (N=15) increased by 58.5 percent (P<0.001) 24 hours after discontinuation of treatment, and by 85.4 percent 30 days later; basal levels of 7.1 to 9.9 μmol per litre (N=15) showed no consistent changes, and the basal levels of 9.9 to 22.1 μmol per litre (N= 16) decreased to 63.9 percent (P <0.005) 24 hours after discontinuation of Sublimed Sulfur, and to 70.7 percent of basal levels 30 days later.

There were no adverse effects on the pulse rate and rhythm, blood pressure and electrocardiograms. There were no significant changes of the complete blood count, urinalysis, erythrocyte folic acid and serum levels of vitamin B12, creatinine, electrolytes, uric acid, glucose, aspartate transaminase, total cholesterol, high-density lipoprotein cholesterol, triglycerides, and calculated levels of low-density lipoprotein cholesterol and total cholesterol/high-density lipoprotein cholesterol ratio. There were no reports of adverse effects by the subjects.

Conclusions Sublimed Sulfur therapy caused a regression towards the mean of basal plasma homocysteine levels and normalized plasma homocysteine to between 7.5 and 8.5 μmol per litre in subjects with normal levels of erythrocyte folic acid and serum vitamin B12. Sublimed Sulfur is an effective treatment for the alteration of plasma homocysteine in medical conditions associated with abnormal plasma homocysteine levels.

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Claims

1. A regimen of treatment with Sublimed Sulfur alters plasma homocysteine levels.

2. Treatment with Sublimed Sulfur as defined in claim 1 increases low levels of plasma homocysteine and decreases high levels of plasma homocysteine.

3. Treatment with Sublimed Sulfur as defined in claim 1 and claim 2 causes plasma homocysteine levels to be maintained within the normal range.

4. Sublimed Sulfur alters plasma homocysteine levels as defined in Claim 1, Claim 2 and Claim 3 when administered together with:

   folic acid,
   folic acid and vitamin B6 (pyridoxine),
   vitamin B12 (cyanocobalamin) and vitamin B6 (pyridoxine),
   vitamin B12 (cyanocobalamin) and folic acid,
   vitamin B12 (cyanocobalamin), folic acid and vitamin B6 (pyridoxine),
   multi-vitamins,
   and foods.

5. Treatment with Sublimed Sulfur as defined in claim 1, claim 2, claim 3 and claim 4 normalizes plasma homocysteine concentrations in

   generalized atherosclerosis,
   accelerated atherosclerosis,
   atherothrombosis,
   coronary atherosclerosis,
   ischemic heart disease,
   angina pectoris,
   coronary thrombosis,
   myocardial infarction,
   atrial arrhythmias,
   ventricular arrhythmias,
   cardiac nerve degeneration due to atherosclerosis,
   carotid atherosclerosis,
   recurrent cerebral embolisation,
   cerebral atherosclerosis,
   transient ischemic attacks,
   stroke,
   atherosclerotic cerebral degeneration,
   peripheral atherosclerosis,
   peripheral ischemia,
   nerve degeneration due to atherosclerosis in peripheral ischemic neuropathy,
   hypertension secondary to generalized atherosclerosis,
   atherosclerotic complications of diabetes mellitus,
   nerve degeneration due to atherosclerosis in diabetic neuropathy,

recurrent thromboembolism,
deep vein thrombosis and pulmonary embolism,
recurrent pulmonary embolism,
venous thrombosis in cancer,
gout,
Alzheimer's disease,
nephrosclerosis,
chronic renal failure,
menopause,
hypothyroidism,
pernicious anemia,
psoriasis,
leukemias,
cancer,
breast cancer,
ovarian cancer,
pancreatic cancer,
osteoporosis due to atherosclerosis,
and the aging process due to atherosclerosis.

INTERNATIONAL SEARCH REPORT

Int. ional Application No
PCT/CA 99/00892

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K33/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 581 972 A (VERDE GIANCARLO U) 9 February 1994 (1994-02-09) claims	1-5
A	EP 0 615 757 A (GRIMBERG GEORGES SERGE) 21 September 1994 (1994-09-21) page 2	1-5
A	FR 2 228 470 A (DEGEMONT MARGUERITE) 6 December 1974 (1974-12-06) claims	1-5
A	US 4 976 970 A (LANDY WADY N) 11 December 1990 (1990-12-11) claims	1-5

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA 99/ 00892

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 1-5 is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte onal Application No
PCT/CA 99/00892

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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